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Role of imaging to choose treatment

Christophe Fermé*, Daniel Vanel†, Vincent Ribrag* and Théo Girinski‡

*Departments of *Medicine, †Radiology and ‡Radiation Therapy, Institut Gustave Roussy, 39 rue Camille Desmoulins, 94805 Villejuif, France*

Corresponding address: Daniel Vanel, Department of Radiology, Institut Gustave Roussy, 39 rue Camille Desmoulins, 94805 Villejuif, France. E-mail: vanel@igr.fr

Abstract

Radiologists perform various examinations at every step of lymphomas. The role of imaging is atypical for a 'classical' oncologic radiologist, as multiple non-radiological criteria are combined to decide on treatments. A good knowledge of the practical use of the results helps the radiologist to seek the useful pieces of information. In treatment evaluation, uncertain complete response is only used in lymphomas. Imaging is changing, with the emergence of PET and whole body MRI but CT remains the key examination today. The WHO criteria are the only ones used to evaluate treatment results on CT, even though the use of PET is increasingly used, with better and better results.

Keywords: *Lymphoma; CT; staging; treatment evaluation.*

Introduction

The management of lymphomas is quite different from the rest of oncology. A good understanding of the practical consequences of imaging findings helps the radiologist to be efficient. Histology is by far the main prognostic factor, and has the highest impact on treatment choices. A follicular lymphoma, even with multiple lesions, may not require any treatment, whereas a limited high grade lymphoma will require very aggressive treatment. Then multiple other criteria, including imaging, are involved in the choice of treatment. Computed tomography (CT) is the main imaging modality, as it is reproducible and widely available. Magnetic resonance (MR) imaging is especially efficient to evaluate bone marrow. Positron emission tomography (PET) has increasing value in the initial staging and evaluation of early effectiveness of treatment.

Definition of criteria for radiologic evaluation

Radiologic pre-treatment evaluation procedures include chest radiographs (posteroanterior and lateral) and CT of the thorax, abdomen, and pelvis. These investigations are needed to define a number of parameters that are of importance in terms of prognosis, and should be taken into consideration when planning treatment.

Extent of disease

The extent of disease is evaluated according to the Ann Arbor staging classification and Cotswolds' revision (Table 1)[1] or St Jude staging system used for childhood non-Hodgkin's lymphoma and adult patients with Burkitt's lymphoma (Table 2).

Among the criteria are:

- The number of peripheral nodal sites involved. Peripheral nodal sites are defined as cervical (one or several anatomic groups), axillary, inguinal or femoral right and left.
- Tumour volume. A mediastinal mass is defined as bulky on a posteroanterior chest radiograph when the maximum width is equal to or greater than one-third of the internal transverse diameter of the thorax at the level of the T5–T6 interspace[2]. A large mediastinal mass is defined as MT ratio $\geq$0.35. This criterion is mainly used for Hodgkin's

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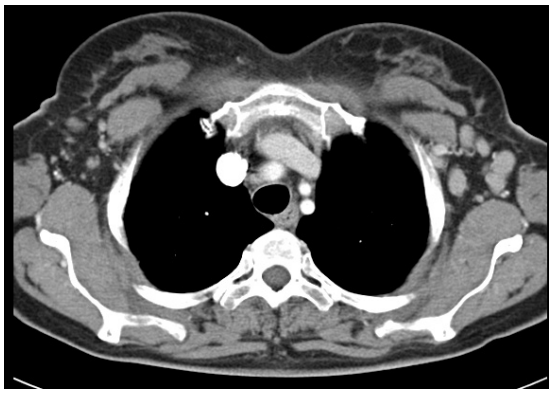
lymphoma. According to Cotswolds' modifications of the Ann Arbor classification, a palpable lymph node or conglomerate node mass must be 10 cm or greater in largest diameter to be recorded as bulky. The nodal and extranodal targets defined for assessment of response are measured bidimensionally according to the WHO criteria[3]. RECIST criteria cannot be used.

Prognostic index and score

A number of prognostic scores are used to define prognosis and to make medical decisions for different entities according to the WHO classification of malignant lymphoma[4].

(a)



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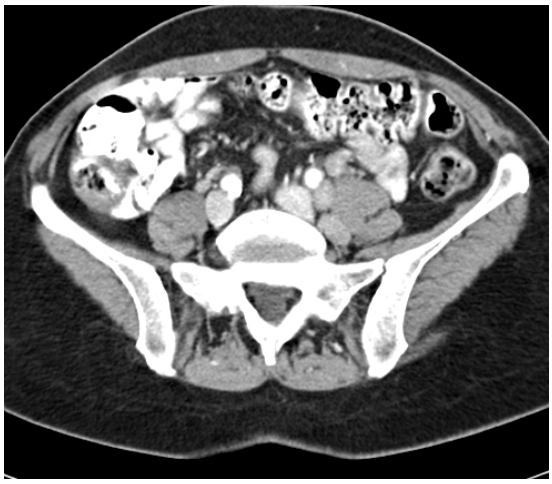
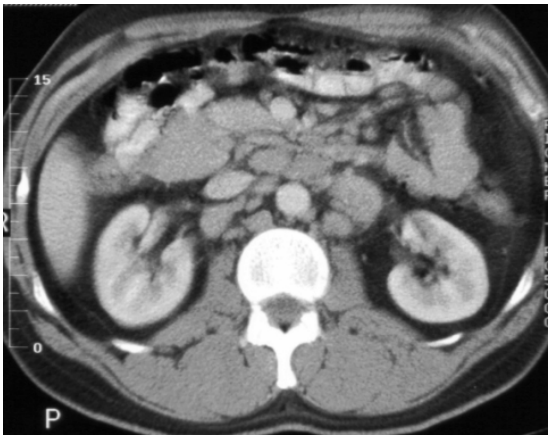


Figure 1 **Follicular lymphoma. Although there are multiple enlarged nodes in the axilla (a) and pelvis (b), no three masses are more than 3 cm in different locations, so imaging results alone are not an indication to treat.**

Hodgkin's lymphoma

Treatment of Hodgkin's lymphoma depends on stage and prognostic factors. For early stage supradiaphragmatic Hodgkin's lymphoma, the European Organization for Research and Treatment of Cancer (EORTC) Lymphoma Cooperative Group have defined prognostic factors and prognostic subgroups[5,6] for clinical trials since 1988 and adopted by the Groupe d'Etudes de Lymphomes de l'Adulte (GELA) since 1993 (Table 3). The International Prognostic Score (IPS) for advanced stage Hodgkin's lymphoma is used to stratify patients with advanced stage disease in ongoing trials. The IPS is based on seven factors: age $\geq$45 years, male gender, stage IV, white blood count (WBC) $\geq 15 \times 10^9$/l, lymphocytes count $<0.6 \times 10^9$/l or <8% WBC, albumin <4 g/dl, haemoglobin <10.5 g/dl[7]. Extranodal involvement is the only factor on radiologic evaluation. The German Hodgkin Lymphoma Study Group (GHSG) adopted very similar prognostic factors to define early and intermediate stages, but does not apply the International Prognostic Score (Table 3). Radiological staging represents only one of the many prognostic factors. It is a little disappointing for the radiologist to represent only one criterion, of no more value than one of the clinical or biological criteria.

(a)



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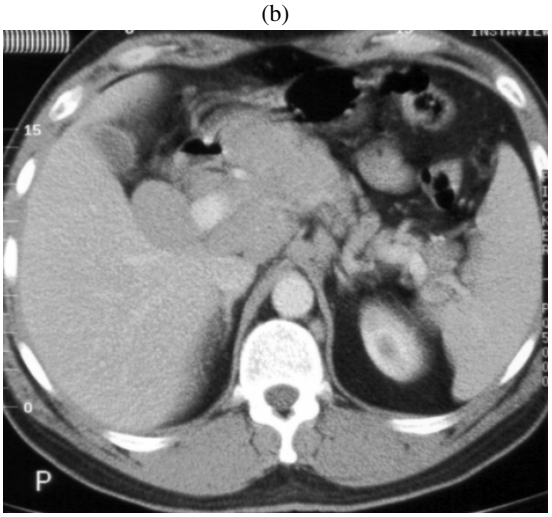


Figure 2 **Follicular lymphoma. Multiple diffuse nodes on CT (a). The mesenteric mass, measuring more than 7 cm in diameter, is an indication to treat.**

Follicular lymphoma

The Groupe d'Etudes des Lymphomes Folliculaires (GELF) criteria have been defined from studies of the GELA[8] as parameters to initiate treatment in patients with untreated follicular lymphoma grade 1, 2 or 3a and were chosen for the Primary Rituximab and Maintenance (PRIMA) ongoing trial (a multicentre, phase III, open-label, randomized study in patients with advanced follicular lymphoma evaluating the benefit of maintenance therapy with rituximab (MabThera®) after induction of response with chemotherapy plus rituximab in comparison with no maintenance therapy.

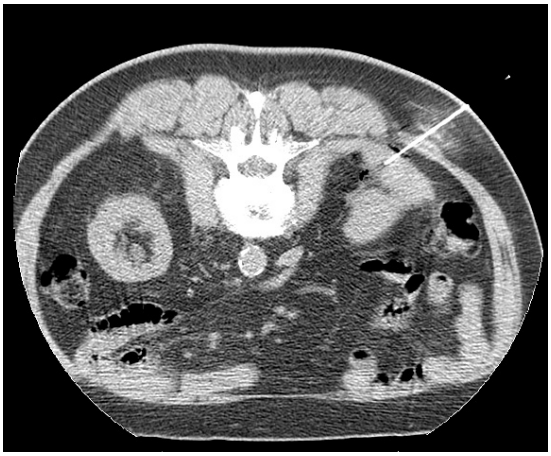


Figure 3 **Retro renal mass appeared in a patient presenting with a low grade lymphoma. CT guided biopsy was performed to look for a higher grade transformation of the lymphoma (in this case, everything actually remained low grade).**

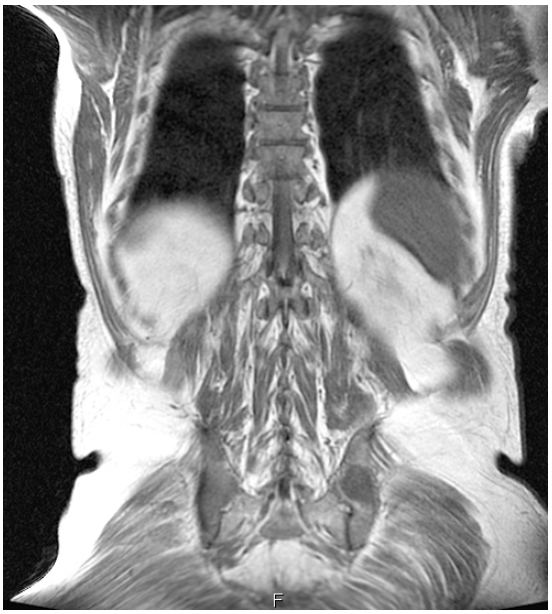
Bulky disease is defined by the presence of one criterion:

- a nodal or extranodal mass $\geq$7 cm in its greater diameter
- or B symptoms
- or increased lactate dehydrogenase (LDH) and β2 microglobulinemia
- or involvement of at least three nodal sites (each with a diameter greater than 3 cm)
- or splenic enlargement
- or compression syndrome
- or pleural/peritoneal effusion.

One of these criteria justifies treatment (and in their absence, no treatment is given) (Figs 1 and 2).

The Follicular Lymphoma International Prognostic Index (FLIPI Score) has been defined after retrospective analysis of different trials[9]. Five independent adverse prognostic factors were selected after multivariate analysis:

(a)



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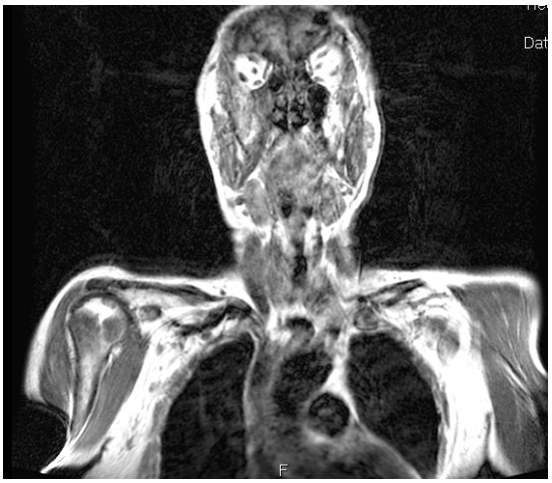

Figure 4 **Whole body MRI performed in the initial evaluation of a lymphoma. T1-weighted images. Chest (a) and pelvis (b) images. Bone marrow involvement of the right proximal humerus and left sacral wing are easily detected.**

1. Age (>60 vs. $\leq$60)
2. Ann Arbor stage (III–IV vs. I–II)
3. Haemoglobin level (<12 g/dl vs. $\leq$12 g/dl)
4. Number of nodal areas (>4 vs. $\leq$4)
5. Serum LDH level (> normal vs. $\leq$ normal)

The nodal areas involved are enumerated for each patient and defined as follows: cervical (pre-auricular, upper cervical, median or lower cervical, posterior cervical or supraclavicular), axillary, mediastinal (paratracheal, mediastinal, hilar), mesenteric (celiac, splenic hilar, hepatic hilar, portal, mesenteric), para aortic (para aortic, common iliac, external iliac), inguinal (inguinal,

femoral), and other (epitrochlear, popliteal). Three risk groups were defined: low risk (0–1 adverse factor), intermediate risk (2 adverse factors), and poor risk (≥3 adverse factors).

Aggressive non-Hodgkin lymphomas

The International Non-Hodgkin's Lymphoma Prognostic Factors Project has identified a predictive model for outcome that has established five independent prognostic factors: age (>60 years adverse), stage I–II vs. III–IV (III–IV adverse), number of extranodal sites (>1 adverse), performance status (low status Eastern Cooperative Oncology Group (ECOG) >2 adverse), serum LDH (elevated level adverse)[10]. The age-adjusted International Prognostic Index (stage, performance status, serum LDH) is applied worldwide to stratify patients into prognostic subgroups.

Burkitt's lymphoma

The Ann Arbor staging system is not well suited to patients with Burkitt's lymphoma, which is predominantly extranodal (bone marrow and/or central nervous system involvement not always accompanied by nodal involvement). The most widely used classification is the St Jude staging system used for childhood non-Hodgkin's lymphoma (Table 2). Staging procedures should be done within 24–48 h because of the rapidity of tumour growth. Peritoneal or pleural effusions are particularly helpful for the diagnosis and should be documented with cytogenetics, immunophenotyping and genotyping. Tumour burden is a prognostic factor and evaluation of tumour size is necessary for restaging under treatment. Magnetic resonance imaging of the head and neck, chest, abdomen, skeleton, and central nervous system (CNS) may be indicated in some circumstances but is not used routinely.

Impact of radiologic evaluation on treatment decision

Initial staging at diagnosis

Hodgkin's lymphoma

In early stage supradiaphragmatic Hodgkin's lymphoma, the standard treatment is a combination of chemotherapy followed by radiotherapy. The number of cycles of chemotherapy (ABVD regimen (adriamycin, bleomycin, vinblastine, dacarbazine) as standard) depends on prognostic subgroups, three cycles for favourable groups and four cycles for unfavourable groups. Radiotherapy is delivered to responding patients and limited to initially involved areas: 'involved fields' radiation therapy.

As the treatment subgroups (unfavourable and favourable) are defined by adverse prognostic factors, a careful evaluation of the extent of disease and tumour size is a condition for a risk adapted strategy: number of cycles of chemotherapy, radiotherapy delivered to all initially involved areas (evaluation of axillary areas on chest CT), and planned doses of radiotherapy delivered according to the response to chemotherapy.

In advanced stage Hodgkin's lymphoma, the standard treatment is chemotherapy alone with ABVD regimen, eight cycles if a complete response or complete response uncertain is achieved after 6 cycles.

Tumour volume as a large mediastinal mass has no impact on the choice of first line chemotherapy, however, the tumour size is measured for the evaluation of response to initial chemotherapy (first evaluation recommended after four cycles).

Follicular lymphoma

The initial evaluation is of importance to identify patients with a small tumour burden and a slow progression of disease for whom a watch and wait policy is recommended by the majority of centres and those with adverse risk factors as previously described who need to be treated. Chemotherapy (cyclophosphamide, vincristine and prednisolone (CVP), CHOP regimen or Fludarabine-based regimens) plus rituximab (MabThera®), a chimeric/human monoclonal antibody that is directed specifically against the B-cell antigen CD20, is considered in many countries as the standard for first-line treatment of patients with follicular lymphoma.

Diffuse large-B-cell lymphoma

The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone) combined with rituximab given in eight cycles is the standard of care for elderly patients (≥60 years old) with diffuse large-B-cell lymphoma[11].

Evaluation of the Ann Arbor stage is the main parameter evaluated on imaging with an impact on the definition of initial treatment based on the age-adjusted International Prognostic Index (Fig. 4).

Burkitt's lymphoma

Treatment protocols based on combination chemotherapy regimens designed for children, consisting of intensive doses of alkylating agents given in combination with methotrexate, vincristine, cytarabine, have been shown to be highly effective for patients with Burkitt's lymphoma, whether adults or children. CNS prophylaxis including intrathecal methotrexate and cytarabine is an essential component of therapy. Treatment subgroups are defined on the basis of bone marrow and/or CNS involvement at diagnosis: patients without bone marrow and/or CNS involvement (stages 1–3 of the St Jude staging system) and patients with bone marrow and/or CNS involvement

Table 1 Ann Arbor staging classification and Cotswolds revision

Stage I	I	Involvement of a single lymph node region.
	IE	Localized involvement of a single extralymphatic organ or site.
Stage II	II	Involvement of two or more lymph node regions on the same side of the diaphragm.
	IIE	Localized involvement of a single associated extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm. Right and left hilum: one area each, independent of mediastinum; number of anatomic nodal areas to be indicated by a subscript (II_4).
Stage III	III	Involvement of lymph node regions on both sides of the diaphragm.
	III_1	Upper abdomen (splenic, hilar, celiac, or portal nodes).
	III_2	Lower abdomen (paraaortic, iliac, mesenteric nodes).
	IIIE	Involvement of lymph node regions on both sides of the diaphragm accompanied by localized involvement of an extralymphatic organ or site[a].
Stage IV	IV	Disseminated (multifocal) involvement of one or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement. The absence or presence of fever $>38\,^{\circ}C$, drenching sweats during the last month, and/or weight loss of 10% or more of body weight in 6 months are to be noted in all cases by the suffix letters A or B, respectively.
	X	Bulky disease, $>1/3$ widening of mediastinum at T5–T6 level, or >10 cm maximum dimension of nodal mass.
	CR(u)	Unconfirmed/uncertain complete remission (residual imaging abnormality).

[a]In FLIPPI, spleen involvement is categorized as stage IV.

Table 2 St Jude staging system used for childhood non-Hodgkin's lymphoma[a]

Stage	Definition
I	Single tumour (extranodal) Single anatomic area (nodal) Excluding mediastinum or abdomen
II	Single tumour (extranodal) with regional node involvement Primary gastrointestinal tumour with or without involvement of associated mesenteric nodes only, grossly completely resected On same side of diaphragm: Two or more nodal areas Two single (extranodal) tumours with or without regional node involvement
III	On both sides of the diaphragm: Two single tumours (extranodal) Two or more nodal areas All primary intrathoracic tumours (mediastinal, pleural, thymic) All extensive primary intra-abdominal disease All primary paraspinal or epidural tumours regardless of other sites
IV	Any of the above with initial central nervous system or bone marrow involvement (<25%)

[a]Patients with more than 25% of blast cells in the bone marrow are considered to have acute-B-cell leukaemia.

who are stratified according to age and CNS involvement because of the toxicity of methotrexate and cytarabine. Appropriate measures for the prevention of tumour lysis syndrome are highly recommended. The role of rituximab is being evaluated in prospective trials.

Response assessments during and after treatment

Response is classified as complete response (CR), complete response unconfirmed (CRu), partial response (PR), stable disease or progressive disease, according to standardized response criteria[12] (Table 4).

The impact of response assessment depends on the planned treatment for the different types of lymphomas.

Hodgkin's lymphoma

In early stage supradiaphragmatic Hodgkin's lymphoma, response is evaluated after initial chemotherapy and before radiation therapy, to confirm the planned radiotherapy for responding patients and the doses of radiation therapy to initially involved areas. Patients with stable disease or progression are treated with salvage therapy.

In advanced stage Hodgkin's lymphoma, an intermediate response evaluation is recommended at the end of the 4th and 6th cycles. Patients who achieve at least a PR at the end of the 4th cycle continue the chemotherapy and are restaged after six cycles. Patients who achieve a CR/Cru after six cycles usually receive consolidation chemotherapy. Patients with a partial response after initial chemotherapy, are submitted to additional investigations (PET scan, MRI, biopsy of

Table 3 Hodgkin's lymphoma, risk factors according to cooperative treatment groups[a]

	EORTC	GHSG	Canada
Risk factors (RF)	(A) Mediastinal mass MT ≥0.35	(A) Mediastinal mass MT ≥0.35	
	(B) Age ≥50 years	(B) Extra nodal site E	(B) Age >40 years
	(C) (A) and ESR ≥50 or (B) and ESR ≥30	(C) ESR ≥50 mm without or ≥30 mm with (B) symptoms	(C) ESR >50
	(D) ≥4 nodal areas	(D) >3 nodal areas	(D) ≥3 sites
Stage			
Favourable (F)	I–II without RF	I–II without RF	I–II without RF
Unfavourable (UF)	I–II with 1 or +RF	I–IIA with 1 or +RF	I–II with RF
Or intermediate advanced	III–IV	IIB with A/B; III–IV	

[a]GHSG, German Hodgkin's Lymphoma Study Group; EORTC, European Organisation for Research and Treatment of Cancer; GELA, Groupe d'Etudes des Lymphomes de l'Adulte; ESR, erythrocyte sedimentation rate; MT ratio, ratio of the largest transverse diameter of the mass to the transverse diameter of the thorax at the level of T5–T6.

Table 4 Response criteria for non-Hodgkin's lymphoma: International Working Group recommendations[12]

Response category	Physical examination	Lymph nodes	Lymph node masses	Bone marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	≥75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥50% decrease	≥50% decrease	Irrelevant
	Decrease in liver/spleen	≥50% decrease	≥50% decrease	Irrelevant
Relapse/progression	Enlarging liver/spleen; new sites	New or increased	New or increased	Reappearance

mediastinal or infradiaphragmatic node or mass) in order to define if a salvage treatment is indicated. Response is evaluated after eight cycles, patients with a partial response and documented active disease are candidates for additional treatment (radiation therapy in the case of localized nodal disease).

Follicular lymphomas

The PRIMA study has been designed to compare the maintenance schedule of one infusion of rituximab every 2 months for 24 months vs. observation until progression, relapse, death or institution of new treatment for follicular lymphoma in patients responding to an induction standard regimen of rituximab plus chemotherapy (CVP, CHOP, fludarabine, cyclophosphamide, mitoxantrone (FCM)). After induction treatment (six or eight cycles of chemotherapy combined with eight infusions of rituximab), responding patients (complete response CR or partial response PR will be randomized to maintenance therapy vs. no further treatment (observation). Patients with stable or progressive disease will be discontinued from study treatment.

Diffuse large B cell lymphomas

The treatment is delivered according to two phases, an induction phase and a consolidation phase. Evaluation of response after the induction phase is performed to identify the responding patients (CR or PR) for whom the consolidation phase is confirmed and patients with stable disease or progression for whom a new treatment is necessary. After the completion of the planned treatment, a final restaging is performed, usually within 4 weeks of the last treatment, to define patients with CR or CRu who are submitted to the follow-up evaluation, and patients with partial response who are submitted to disease documentation (PET scan and/or histological), in order to decide a new anti-lymphoma therapy (Fig. 3).

Burkitt's lymphoma

Response to the initial cyclophosphamide, vincristine, prednisone (COP) regimen is a prognostic factor and needs to be evaluated early at day 7 by clinical examination and ultrasonography of an abdominal mass. Response must be evaluated further after the first cycle of consolidative chemotherapy. Surgical resection is indicated for patients with residual mass after consolidative chemotherapy, in order to define salvage treatment with intensive chemotherapy and autologous stem cell transplant for patients with documented partial response.

Conclusion

Treating lymphoma combines multiple criteria based on years of trials. Although they may look very strange, they are probably efficient. Radiology plays a well-defined role among those criteria. Their extensive knowledge will

allow the radiologist to be an active and useful part of the team in charge of the patient.

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